Medical Staff Conference

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Hypophosphatemia

These discussions are selected from the weekly staff conferences In the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Assistant Professor of Medicine, and H. David Watts, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. WILLIAMS:* *Today our Grand Rounds will be devoted to a finding often noted in our patients but rarely understood or evaluated fully: hypophosphatemia. Our discussant is Dr. Faith Fitzgerald, Assistant Professor of Medicine and Assistant Chief of Medical Service at San Francisco General Hospital.*

DR. FITZGERALD:† Thank you, Dr. Williams. The clinical problems associated with hypophosphatemia have only lately burst upon the medical ken. In the past, mention of phosphorus generally had to do with its increase in renal failure and its role as a pallid, usually well-behaved and predictable companion of calcium.

The attention now given to phosphorus in its own right has, in part, to do with its more frequent routine determination in automated systems and, most particularly, with the strong association of large numbers of hypophosphatemic states with iatrogenic maneuvers. As we have become more therapeutically vigorous, we have again created or magnified a disorder to the point where its deleterious effects become evident in numbers impossible to ignore.

Phosphorus depletion from dietary deficiency in nature is essentially unknown, as phosphorus is widely distributed in ordinary food. This makes teleological sense, insofar as phosphorus plays a major role in the structure of all mammalian cells and is a participant in the most fundamental reactions of aerobic and anaerobic metabolism.

In what clinical circumstances ought we to suspect potential hypophosphatemia? Hypophosphatemia, by which I mean serum phosphorus levels less than 3 mg per 100 ml, has been caused by: binding of phosphorus in the gut by nonabsorbable antacids; hemodialysis against phosphate-poor solutions (almost invariably in combination with antacid therapy); starvation and cachexia; acute and chronic alcoholism; hyperalimentation with phosphate-poor mixtures; intravenous administration of carbohydrates; hyperparathyroidism; rickets; osteomalacia; renal tubular defects; pregnancy; hypothyroidism; vitamin D excess and deficiency; alkalosis; acidosis,

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malabsorption; liver disease; hypokalemic and hypomagnesemic states, Gram-negative and Gram-positive sepsis; acute myocardial infarction; gout; administration of sex hormones, catecholamines and thiazides; diabetes, and genetic hypophosphatemia (Table 1).

Serum phosphorus levels usually remain between 3 and 4.5 mg per 100 ml with a diurnal variation and a postcibal mean fall of 0.25 mg per 100 ml below fasting levels in a normal person. This presumably occurs by the same mechanism by which intravenous carbohydrate loads induce a reduction in serum phosphate: phosphorus accompanies glucose entry into cells. It is evident that the serum phosphorus levels in a specimen drawn in the emergency room may be significantly higher than in one drawn several hours later on the ward if, in the meantime, intravenous administration of dextrose has been continuing. It may be by this mechanism that intravenous hyperalimentation induces such profound falls in serum phosphorus.

It is pertinent, particularly in the last regard, that the hypophosphatemia which normally accompanies the disposal of glucose is notably accentuated by fasting. Starvation, as in chronic alcoholics or candidates for hyperalimentation, may cause shunting of a carbohydrate load from liver to muscle. Perhaps, in the fasting state, less glucose enters the liver as glycogen and more is disposed of via glycolysis in peripheral tissues, using up serum phosphorus in the process.

Certainly we see our share of starved patients and of alcoholics with liver disease. How common is hypophosphatemia? In Britain, where these conditions are less frequently seen than at a county hospital in San Francisco, a 1972 study[1] showed that in 2 percent of all admitted patients, levels of serum phosphates were less than 2 mg per 100 ml. At the Oklahoma City Veterans Administration Hospital, it was found that in 42 percent of 106 patients admitted with the diagnosis of acute alcoholism, serum phosphorus levels were less than 3 mg per 100 ml, with values less than 2 mg per 100 ml in 10 percent.[2] I would anticipate that there might be similar findings in any hospital having a large number of malnourished alcoholic patients. It is not a statistically inconsequential problem.

What sort of clinical problem is it? What difference does it make? Several manifestations associated with hypophosphatemia have been described. I have taken the liberty of dividing these syndromes, scattered throughout the literature predominantly as case reports, into four major categories: neuromuscular, hematologic, hepatic and skeletal (Table 2).

TABLE 1.—*Hypophosphatemia: Causes and Associations*

Antacids: binding of phosphorus in the gut
Hemodialysis: against phosphate-poor bath
Starvation/Cachexia
Alcoholism
Hyperalimentation: with phosphate-poor solution
Carbohydrate administration: most pronounced intravenously
Hyperparathyroidism
Rickets/Osteomalacia
Renal tubular defects
Pregnancy
Hypothyroidism
Vitamin D deficiency or excess
Alkalosis
Acidosis
Malabsorption
Liver disease
Hypokalemia
Hypomagnesemia
Sepsis: Gram-negative and -positive
Acute myocardial infarction
Acute gout
Estrogens/Androgens
Catecholamine administration
Hyperventilation
Diabetic ketoacidosis
Genetic hypophosphatemia
Thiazide diuretics

Neuromuscular Manifestations

In Lotz's seminal paper in 1968[3] he described symptoms in patients rendered hypophosphatemic by phosphate binding magnesium-aluminum hydroxide antacids. The symptoms of his patients were like those noted earlier in experimental phosphate depletion studies in animals: weakness, malaise, anorexia, bone pain, joint stiffness and intention tremor. The severity of distress correlated with the level of serum phosphorus, with symptoms beginning at levels less than 2 mg per 100 ml. He suggested that the debility in some patients with hyperparathyroidism (bone and muscle pain, neurologic abnormalities and malaise) might be attributable to phosphate depletion rather than to the more commonly considered calcium abnormalities.

In another report[4] a young girl rendered hypophosphatemic by antacids and hemodialysis showed progressive severe muscle weakness involving the extremities, neck, and muscles of mastication, articulation and respiration. Anisocoria, ballismus and hyporeflexia were noted. Results of

electroencephalographic, electromyographic and nerve conduction studies were all abnormal, but returned to normal as serum phosphate rose.

Muscle contraction is known to be intimately dependent upon adenosine triphosphate (ATP) and organic phosphate compounds in muscle. Doctors Klock, Williams and Mentzer at San Francisco General Hospital recently published data[5] highly suggestive of a metabolic defect in muscle and liver in hypophosphatemia, with inhibition of glycogenolysis or glycolysis consequent to phosphate depletion. In their study, patients in whom serum phosphorus levels were below 0.5 mg per 100 ml were found to have abnormal responses to both ischemic exercise and to glucagon administration—suggesting interference with glycogenolysis in both liver and muscle. Both responses were returned to normal with correction of the hypophosphatemia.

TABLE 2.—*Hypophosphatemia: Syndromes and Abnormalities**

System and Syndrome	*Abnormality*
Neuromuscular	
Muscle weakness	Decreased CNS ATP
Anorexia	Inhibition of muscle
Intention tremor	Glycolytic pathways
Paresthesias	
Coma	
Convulsions	
Anisocoria	
Ballismus	
Hyporeflexia	
Ataxis	
Death	
Hematologic	
Erythrocytes	
Hemolytic anemia	Decreased ATP
Decreased oxygen release	Decreased 2,3-DPG
	? Abnormal membrane lipids
Leukocytes	
Decreased chemotaxis	Decreased ATP
Decreased phagocytosis	? Abnormal membrane lipids
Decreased killing	
Platelets	
Decreased clot retraction	Decreased ATP
Decreased survival *in vivo*	
Hepatic	
? Failure of compensatory 2,3-DPG—hepatic hypoxia	
Correlation with hepatic coma	
Skeletal	
Osteomalacia	Negative calcium balance with reabsorption
Arthritis	

*CNS = central nervous system, ATP = adenosine triphosphate, 2,3-DPG = 2,3-diphosphoglycerate.

A 50- to 80-percent decrease in brain cell ATP has been shown in hyperalimented hypophosphatemic dogs, with concurrent ataxia, convulsions and death.[6] Coma and convulsions in hypophosphatemic patients, again in the setting of hyperalimentation, have been reported.[7]

Hematologic Syndromes

Hematologic correlates of the hypophosphatemic state have been more extensively studied than any other. Abnormalities described include defects in red cells, leukocytes and platelets.

Erythrocytes

Two major categories of erythrocyte impairment have been studied in association with hypophosphatemia: those of structure and those of function. In mature red cells, ATP generation depends on the anaerobic metabolism of glucose (Figure 1). Adenosine triphophate synthesis occurs, mainly in the erythrocyte membrane, during the conversion of glyceraldehyde-3-phosphate to 3-phosphoglycerate. The source of phosphate for phosphorylation of glyceraldehyde-3-phosphate (and subsequently, adenosine diphosphate [ADP]) is the extracellular phosphate pool, from which inorganic phosphate enters into the membrane reaction predominantly by passive diffusion. Hence, changes in the concentration of intracellular phosphate can be produced by alterations of

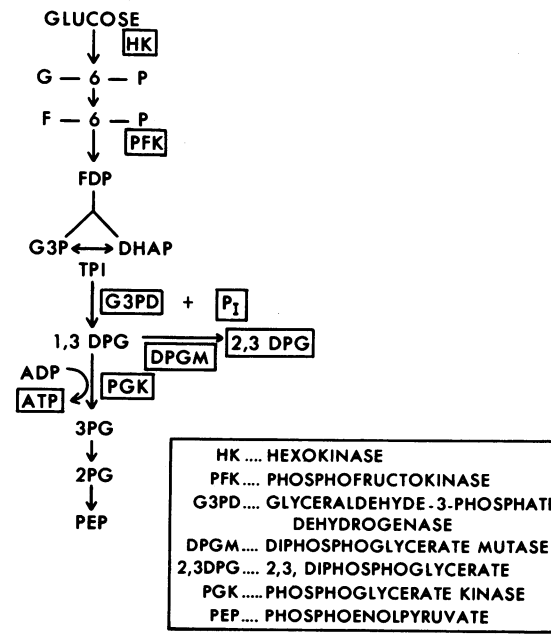

Figure 1.—The Embden-Meyerhof pathway of erythrocyte glycolysis. Abbreviations are shown in the figure.

extracellular inorganic phosphate. An increase of serum phosphate, as in renal failure, stimulates glucose uptake and glycolysis at a number of points in the Embden-Meyerhof pathway; a decrease in extracellular phosphate has been clearly shown to have the converse effect, with a subsequent decrease in ATP production. The regulation appears most influential at the glyceraldehyde-3-phosphate dehydrogenase step, possibly because a considerable proportion of red blood cell glyceraldehyde-3-phosphate dehydrogenase is membrane bound and derives its substrate inorganic phosphorus directly from the extracellular inorganic phosphate pool.

Adenosine triphosphate is necessary for maintenance of erythrocyte membrane integrity and deformability and thus is very influential in determining red blood cell life span. *In vitro* studies show that ATP must be depressed to about 15 percent of normal levels before membrane rigidity and morphologic changes (spherocytosis) are detectable.[8] Actin and myosin-like microfilamentous proteins present in red blood cell membranes may be responsible for normal erythrocyte shape and plasticity. Insofar as actin and myosin in skeletal muscle requires ATP for controlled contraction, it is tempting to speculate that a similar phenomenon in hypophosphatemia may give rise to both red cell rigidity and to muscle weakness. Another possibility is that alterations in glycolysis affect the balance and stability of membrane lipids in red blood cells or that with severe ATP deficiency the sodium-potassium pump is itself compromised.

Whatever the mechanism, severe but reversible hemolytic anemia has been well documented in patients with profound hypophosphatemia (less than 0.2 mg per 100 ml, generally). Red blood cell ATP and 2,3-disphosphoglycerate were notably depressed (to 11 and 30 percent of normal, respectively). Striking reduction in erythrocyte ATP was associated with microspherocytic morphology, increased rigidity and diminished survival of the affected cells (^{51}Cr-survival time *in vivo* of one-fifth normal). All returned to normal after parenteral phosphate supplementation.[8]

Fortunately, despite pronounced reductions in serum phosphate, red blood cell ATP is rarely observed to fall much below 40 percent of normal, a condition tolerated remarkably well by the otherwise normal erythrocyte. The potential threat for red blood cell injury is compounded, however, by truly profound hypophosphatemia (during which red blood cell ATP may fall to less than 15 percent of normal) or by combinations (as in alcoholic or septic patients) of moderate ATP depletion and other disturbances of red blood cell integrity or of the microcirculation.

In addition to its role in the structural integrity of red blood cell membranes, serum phosphorus is intimately involved in basic erythrocyte function. The rate of red blood cell glycolysis and the passage of the intermediate 1,3-diphosphoglycerate through the glycolytic appendage (Rapoport-Luebering pathway) regulates intraerythrocytic 2,3-diphosphoglycerate concentration. Dr. George Sheldon of our own institution and others have done extensive work on the influences and consequences of hypophosphatemia on 2,3-diphosphoglycerate; specifically, on its integral association with the oxyhemoglobin dissociation curve and thus tissue oxygenation.[9]

Although the affinity for hemoglobin and the effect on oxygen binding of ATP and 2,3-diphosphoglycerate are similar, in red cells, the presence of three times as much 2,3-diphosphoglycerate as ATP makes the former quantitatively more important in this regard. The presence of 2,3-diphosphoglycerate and ATP decreases the affinity of hemoglobin for oxygen; the lower the 2,3-diphosphoglycerate, therefore, the greater the binding between oxygen and hemoglobin and the less readily released is oxygen to tissues (Figure 2).

In studies on patients hyperalimented without phosphate supplement, Dr. Sheldon found profound hypophosphatemia developing within ten days. Low serum phosphorus was associated with a

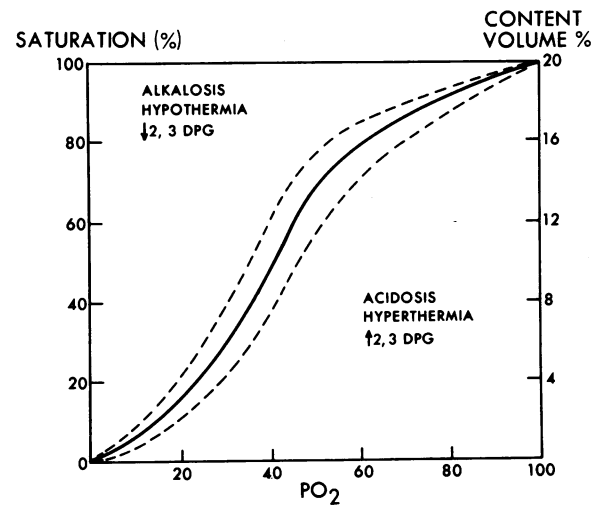

Figure 2.—Oxyhemoglobin dissociation and the effects thereon of acidosis, alkalosis, hypo- and hyperthermia, and 2,3-diphosphoglycerate (2,3-DPG).

measured decrease in red cell 2,3-diphosphoglycerate and ATP and with consequent increase in hemoglobin affinity for oxygen. This "shift to the left" of the oxyhemoglobin dissociation curve has been demonstrated in phosphate depletion in the absence of alkalosis and hypothermia (other factors increasing hemoglobin-oxygen binding) and in spite of factors which, in patients with normal serum phosphatic concentrations, "shift the curve to the right": fever, acidosis and liver disease.

With correction of serum phosphate concentration, red cell metabolism and oxygen release returned to normal. It is of interest that the fall in 2,3-diphosphoglycerate was generally more profound than that of ATP in hypophosphatemia; with phosphate repletion, 2,3-diphosphoglycerate regeneration took precedence over ATP repletion.[9]

Because of the known effects of 2,3-diphosphoglycerate depletion on tissue oxygenation, it has been proposed that the neuromuscular effects of hypophosphatemia are but those of tissue anoxia. However, Klock's data on muscle cell metabolic dysfunction in hypophosphatemia,[5] the demonstrated ATP depletion of central nervous system cells[6] and the observation that some patients with phosphate depletion are notably symptomatic at levels of tissue oxygenation well tolerated in chronically anemic patients suggest that the issue may be more complex.

Leukocytes

Another major hematologic abnormality of potential extensive consequence is the leukocytic dysfunction of hypophosphatemia. Severe hypophosphatemia induced by hyperalimentation in dogs resulted in a 50-percent depression of chemotactic, phagocytic and bactericidal activity of their granulocytes.[10] Concomitant reduction in white cell ATP was confirmed. The motility defect was corrected if cellular ATP was repleted by phosphate supplement of the animals *in vivo* or by *in vitro* incubation of the white cells in adenosine and phosphate. Functionally significant leukocyte ATP depletion has been shown at serum phosphate levels of 1 mg per 100 ml or less.

Phagocytes require ATP to form phagocytic vacuoles, the initial event in pathogen phagocytosis. The contractile apparatus in the granulocytic membrane responsible for amoeboid movement and pseudopod formation presumably requires ATP for actin activated myosin. Serum phosphorus may also play a role in the synthesis of organic phosphorus compounds required during phagocytosis, or for membrane synthesis.

It is well known that bacteremic and fungemic episodes are common in hyperalimented patients, a product of a prolonged indwelling line infusing delicious bacterial culture medium into a cachexic patient. Now add to this situation the potential for hypophosphatemic leukocyte dysfunction. In one study directed to this point, there was evidence of infection in 13 of 18 hypophosphatemic hyperalimented patients compared to but one of ten patients with normal phosphate levels.[10]

This phenomenon may play a role in the infection rate, notoriously high, in alcoholic, diabetic ketoacidotic and steroid cum antacid-treated patients—in all of whom there are other recognized states of white blood cell dysfunction in addition to the propensity to hypophosphatemia.

Platelets

The influence of hypophosphatemia on coagulation has received scant comment in the literature. Here, as elsewhere, phosphate depletion is villainous. Yawata and co-workers found that hypophosphatemic dogs hemorrhaged massively, with absent clot retraction and one-fourth normal ^{51}Cr platelet survival.[6] Platelet ATP depletion has been documented in hypophosphatemic states. Compound this with the thrombopathy of an alcoholic or a uremic patient, or note that many hypophosphatemic patients become so by overenthusiastic use of antacids given *because* they are bleeding. Realize also that if it is necessary to give a transfusion to a hypophosphatemic patient, the blood given may be bank blood, low in platelets and (if stored in low-phosphate anticoagulants) low in erythrocyte 2,3-diphosphoglycerate as well. We should, I think, pay more attention to serum phosphate levels in our bleeding patients.

Hepatic Syndromes

Of particular interest to us in this hospital are the data on the association between hepatic disease and hypophosphatemia. Most of those patients we see with liver disease here are chronic alcoholics, who have ample opportunity for hypophosphatemia. They are starved; some malabsorb from pancreatic disease. We give them intravenous glucose; they are often hypokalemic (which has been associated with a renal tubular phosphate leak) leading to an alkalotic state. Acute metabolic or (if they are hyperventilating from their withdrawal or liver disease) respiratory alkalosis

depresses plasma phosphorus, perhaps by shifting it into cells. Hyperphosphaturia and hypophosphatemia may follow the magnesium depletion which develops after prolonged ethanol ingestion.[2] Catecholamines, released in withdrawal, can lower serum phosphorus. Or if a patient is septic, phosphorus may fall. If a patient is acidotic from lactate or ketones, a compensatory phosphaturia may deplete him.

In an attempt to find out why patients with cirrhosis sometimes show hepatic decompensation under maximum therapy in the hospital, Rajan and co-workers studied serum phosphorus in liver disease.[11] He found that hypophosphatemic patients with cirrhosis tended to undergo greater hepatic decompensation than did patients with normal phosphate levels. He postulated that phosphate depletion, by inhibiting the normal compensatory increase found in erythrocyte 2,3-diphosphoglycerate in cirrhosis, contributed to greater hepatic hypoxemia. This—hepatic tissue hypoxemia caused by the "left shift" of the oxyhemoglobin dissociation curve in the presence of decreased 2,3-diphosphoglycerate—therefore could be responsible for progressive liver injury in malnourished alcoholic patients.

An association between the hypophosphatemic state and hepatic coma has been suggested. In one series, the postulate was that the hypophosphatemia was *caused by* the hepatic failure (both alcoholic and nonalcoholic). The speculation was that the hypophosphatemia represented phosphate shifts from extra- to intracellular space in buffering of the respiratory alkalosis of hepatic coma with resultant increased anaerobic glycolysis during hepatic coma with resultant increase in utilization of high energy phosphate bonds, thus consuming phosphorus.[12]

Skeletal Manifestations

Considering the role of phosphate in bone, it is not surprising that bony integrity may be compromised by phosphate depletion. A group at Kaiser Hospital in San Francisco recently reported four patients presenting with striking rheumatologic symptomy: large joint arthralgias, inflammatory arthritis and clinical-roentgenographic sacroiliitis so severe as to be initially misdiagnosed as ankylosing spondylitis. The patients all showed symptomatic improvement with correction of hypophosphatemia.[13]

Osteomalacia of severity sufficient to produce pathologic fractures has been noted in antacid-induced hypophosphatemia. The independence of this state from parathormone has been shown by its occurrence in several patients with surgically-caused hypoparathyroidism. Lotz and others have amply documented the physiologic response of the organism to hypophosphatemia.[14]

Physiologic Response to Hypophosphatemia

Rapid, profound decrease in urinary phosphorus

The decrease in urinary phosphorus in patients with hypophosphatemia is impressive. Essentially complete renal conservation occurs with losses which are extremely small relative to total body phosphorus. Clearance studies show that conservation exceeds that anticipated from decreased serum phosphate delivery to kidney alone. It has been suggested that there might exist an as yet undescribed "phosphorus-retaining" hormone, or that intratubular cell phosphate might be directly regulatory.

Hypercalciuria to values four to six times those in normal controls

In hypophosphatemia, hypercalciuria is of sufficient degree to produce a negative calcium balance. Some of the excreted calcium clearly comes from the reabsorption of bone, and no doubt contributes to the osteomalacia of hypophosphatemia. The hypercalciuria is reduced with phosphate repletion. Its dramatic presence has led to speculation that a chronically hypophosphatemic patient may have increased risk for nephrolithiasis.

Increased gastrointestinal absorption of calcium

Gastrointestinal absorption of calcium, in combination with bony reabsorption, is of sufficient magnitude to normalize serum calcium in surgically hypoparathyroid patients in the absence of vitamin D therapy. All of these effects are independent of parathyroid hormone.

These physiologic responses to hypophosphatemia become important in that they may lead to confusion with hyperparathyroidism: note that increased serum and urine calcium, decreased serum phosphorus, neuromuscular and bony complaints are common to both. If all occur in a patient with ulcer, the surgeon may be anxious to explore this classic case for parathyroid adenoma rather than simply decreasing the patient's antacid intake.

Similarly, a uremic patient's "metabolic bone disease" and "uremic neuropathy" may be relieved by tempering the vigor of antacid and hemodialytic therapy such that serum phosphate

is normalized. The use of antacids as prophylaxis for ulcer in patients on steroids may lead to phosphorus depletion, with bone disease or infection resultant from both steroids and hypophosphatemia.

Should we treat hypophosphatemia in the absence of symptoms? Certainly the data seem sufficiently impressive to suggest that we ought in all circumstances to prevent or correct those factors known to cause the hypophosphatemic state. Chances are, the serum phosphorus will then return to normal over the next several days without specific therapy.

In the face of manifest signs, symptoms or defects such as have been described, or with a serum phosphorus less than 1 mg per dl, my prejudice now is to treat. Regimes described in the literature include: for those patients able to take it by mouth, Phospho®-Soda (Fleet) 15 to 30 ml (80 to 160 mEq of phosphate) three times daily. If parenteral medication is required, monobasic potassium phosphate, 60 mEq administered intravenously three times a day, has been used with success.[5] The clinician must watch for a reciprocal lowering of serum calcium levels when phosphate is given (remembering that these patients are in negative calcium balance). Dairy food and other high calcium-phosphorus foods in the diet seem safest.

The teleological wisdom of nature was applauded when she guarded against dietary phosphate deficiency. Yet, given the fundamental role of ATP and organic phosphate compounds in living organisms, serum phosphorus seems most unteleologically vulnerable when one considers that it is presumably available in large quantities in bone. The great mystery, for such it remains, revolves around the question of where the phosphorus goes when it disappears from serum. The rapidity of change (hours to days) in the absence of urinary phosphate loss and, more telling yet, the return to normophosphatemia in the absence of supplementation in alcoholics, hyperalimented, antacid-treated, hemodialyzed and septic patients implies rapid fluxes between the intra- and extracellular spaces. Yet each investigator, working with his own set of cells, has presumed that the phosphorus so evidently missing from his system has gone into another. But in the absence of renal and gut phosphate loss (which are genuinely quantitatively insufficient to explain the majority of hypophosphatemic states) all tissues so far closely examined in hypophosphatemia have been phosphate deficient: erythrocytes, leukocytes, platelets, muscle, brain. We must await future study to answer these intriguing questions.

DR. WILLIAMS: *Thank you, Dr. Fitzgerald, for a very fine review. Dr. George Sheldon is with us today and, as noted by Dr. Fitzgerald, he has done a great deal of investigative work in this field. Dr. Sheldon, would you care to make any comments? We would be particularly interested in your thoughts on when and how to treat.*

DR. SHELDON:* I enjoyed very much hearing the excellent analysis of low phosphate problems. I have also enjoyed the interphase between the medical, surgical and pediatric services—each of which has looked at these problems from a different perspective. I think we are evolving some fundamental ideas about the significance of low phosphate syndromes.

One central question relates to whether low phosphate syndromes are purely an indirect effect of the well-documented change in red cells, and presume tissue hypoxia which comes from alterations in glycolytic intermediates such as ATP and 2,3-diphosphoglycerate. There is no question that as serum phosphate goes up and down, the glycolytic rate of red cells also increases or decreases in direct relation to serum inorganic phosphate levels. Unless phosphate levels are quite low (less than 1 mg per 100 ml) these changes do not become profound and one is reluctant to attribute all low phosphate symptoms to red cell deficiency. Although the red cell is a very specialized cell with no nucleus or mitochondria, it, in some way, is a biological biopsy specimen for other cells of the body. I think one may assume that if abnormalities are occurring in red cells secondary to low phosphate, some of these metabolic aberrations may be occurring in other cells of the body. This is a syndrome which relates to the importance of phosphate derivatives not only for energy metabolism but also for repletion of foodstuffs that occur throughout the entire organism.

One needs to separate catabolic versus anabolic low phosphate syndromes. Most instances reported which describe low phosphate syndromes are in patients who are nutritionally depleted for a variety of reasons. The low phosphate syndrome secondary to total parenteral nutrition is somewhat different from that associated with specific catabolic illnesses, such as uremia. A patient re-

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ceiving total parenteral nourishment (TPN) is actively anabolizing dextrose and protein split products or amino acids, presumably to rebuild muscle mass, replace hepatic glycogen, and if excessive, may actually rebuild his fat sources. When anabolism is established, cellular requirements for potassium, phosphate, magnesium and other nutrients increase. We have found that an anabolic patient requires 20 mEq of potassium dihydrogen acid phosphate for every 1,000 nonprotein kilocalories. If this is administered to patients along with parenteral nutrition, serum inorganic phosphate levels will remain quite normal. If phosphate is given in excess of this, an incremental rise in serum inorganic phosphate levels will occur. If no phosphorus is given, a rapid drop in serum inorganic phosphate will occur, and if less than 20 mEq of potassium dihydrogen phosphate for every 1,000 kilocalories is administered, a slow but definite decline in serum inorganic phosphate levels will result.

The clinical application of this would seem to be relatively simple. Adequate phosphate to cover caloric intake needs to be provided. The scientific and biochemical aspects of this are more complex. Probably a minimal drop in serum inorganic phosphate is not harmful, and possibly elevation in inorganic phosphate may be helpful. We currently lack the answers to these questions.

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